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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,649	09/14/2000	Zaid Jayyosi	02481.1690	1144

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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	**PAPER NUMBER**
1624	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/662,649	Zaid Jayyosi et al
Examiner	**Art Unit**
Sudhaker Patel	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 6, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 8, 15, 29-31, 53-59, 61-66, 91, 92, and 96-103* is/are pending in the applica

4a) Of the above, claim(s) *8 and 97-101* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 15, 29-31, 53, 54, 91, 92, 96, 102, and 103* is/are rejected.

7) ☒ Claim(s) *55-59 and 61-66* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The claims under consideration are the claims 1,2,8,15,29-31,53-59,61-66,91,92,96-103,

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/6/02 has been entered.

(I). Restriction/election: Applicants had elected invention of Group XII drawn to Formula (I)(= **ArI**-[CH(R1)(R2)]a-**A** - [CH(R3)(R4)]b- **ArII** - [CH(R5)(R6)]c- **B** - [CH(R7)(R8)]d- **E** - **Z**), and the species of compound of Example 51 cited on page 95 of specification, lines 12-17 i.e. 2-Methyl-6-(3-(2-phenyl-oxazol-4-ylmethoxy)-propoxymethyl)-benzoic acid, wherein the variables are:

Ar I = heterocycle optionally substituted;

Ar II = phenyl, optionally substituted;

A = -O-(R15 R16)g-O-;

B & E = Chemical bond;

Z = non-heterocycle;

c and d = zero;

a and b = 1;

R1-R4 = H/halogen/alkyl.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination. Portion from MPEP is provided for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.
>
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a non-elected species, the Markush-type claim shall be rejected and claims to the non-elected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all non-elected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species was not found in the prior art. When the search was expanded to species wherein ArI is heteroaryl (optionally substituted); a=1; b =1, art was found. As per the guidelines above, the exmination was limited to the compounds of formula as shown in claim 1 wherein a/b = 1; ArI = Heteroaryl only. Other definitions of ARI i.e. fused arylheterocylenyl, fused arylheterocyclyl, fusedheteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused

heteroarylheterocyclenyl, or fused heteroarylheterocyclyl and also all other definitions of the other variables from the generic claims are held withdrawn from consideration. Claim 8 wherein a and b = 0; claim 97, and claims 98-101 dependent on this claim wherein a = 1, b = 0 are additionally withdrawn from consideration under 37 CFR 1.142(b). as being drawn to non-elected subject matter.

The restriction/election is deemed to be proper and is made FINAL.

(II). ***Claim Objections***

Claim 30 is objected to because of the following informalities: Line 4 reads as "indolinyl oxazolyl"; oxadiazolyl isoxazolyl". It is not very clear as to what applicants want to present. Correction is suggested by inserting "comma".

(III). ***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by

> another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-2,15,29-31,53,91,92,102,103 are rejected under 35 U.S.C. 102(e) as being anticipated by Hawkins et al(U.S.P. 6290973 dated 9/18/00 claiming priority US 1999-118131P dated 2/01/1999). See the compounds encompassed by the formulae in column 61, lines 35-45.

(IV). ***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 54 is rejected under 35 U.S.C. 112, para one because the specification, while enabling as a method of treating atherosclerosis, does not reasonably provide enablement for other diseases encompassed by the instant claim as a method of treating a patient suffering from a physiological disorder capable of being modulated by a compound according to claim 1 having PPAR ligand binding activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

The specification on pages 1-4 discloses the compounds to be useful as PPAR ligand receptor binders and their use as agonists or antagonists associated with that activity.

The assay method(s) provided on pages 118-120 disclose that "the activity of the compounds as PPAR alpha modulators may be examined in several relevant vitro and vivo preclinical assays....with a known PPAR alpha modulator.." . Applicants remain silent about the actual test results.

There is no demonstration for the ability to treat a patient suffering from any and all physiological disorder capable of being modulated by a compound according to claim 1 having PPAR ligand binding activity, comprising a step or process of administering to the patient a pharmaceutically effective amount of the compound.

Compound and its pharmaceutically acceptable salts, N-Oxide, a hydrate or a solvate thereof as recited in the claims reads on all such moieties regardless of complexity of structure and point of attachment to the heterocyclic core for which there is insufficient teaching regarding how to use the claimed method with all the possible compounds encompassed by the genus. There is undue burden involved for one skilled in the art in using the compounds instantly claimed in the instant therapeutic use. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their combinations as outlined above, will have ability to generate the compounds either in vivo &/or in vitro by one or more processes/method(s). Applicants have not provided any data pertinent to "in vivo" tests, and also no nexus has been provided to show how the in vitro data correlates to it.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:

(1). The nature of invention;

(2). the state of prior art ;

(3). the predictability or lack thereof in the art;

(4). the amount of direction or guidance present;

(5). the presence or absence of working examples;

(6). the breadth of the claims, and

(7). the quantity of experimentation needed.

Applicants have not provided any competent evidence or disclosed test results that are highly predictive for the pharmaceutical use for the treatment of physiological disorder related to PPAR ligand activity of the compounds as claimed herein. Pharmacological activity related to physiological disorder in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, " the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24(CCPA 1970).

In this respect following data has been considered for a few disorders:

a). Current state of large scale clinical trial for PPAR ligand:

Molavi et al(PuBMed Abstr.;12000972; J. Cardiovasc Pharmacol Ther 2002 Jan;7/1:1-8) states that "PPAR ligand appear to be promising agents in limiting atherosclerosis; however

large-scale clinical trials are required to assess their safety and efficacy before they can be added to the clinicians' arsenal of antiatherosclerotic agents".

b). Undesirable side effects during insulin-sensitizing action:

Picard et al(PuBMed Abstr.;12055342:Annu Rev Nutr 2002; 22:167-197) clearly state that" Although relatively potent for their insulin-sensitizing action, currently marketed PPAR gamma activators have some important undesirable side effects... Data from human genetic studies and from PPAR gamma heterozygous knockout mice indicate....could paradoxically improve insulin sensitivity. These findings suggest that modulation of PPAR gamma activity by partial agonists or compounds that effect cofactor recruitment might hold promise for the treatment of insulin resistance".

Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

Based on the rejections already discussed in earlier Office Action paper #12 dated 2/6/02, and the facts provided as above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for a physiological disorder.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use as a method of treatment as claimed herein.

In view of the breadth of the claims, the nature of the invention, the unpredictability of ligand binding activity in general, and lack of working examples regarding the activity of the compounds, one having ordinary skill in the art would have to undergo an undue experimentation to use the invention commensurate in scope with the claims.

(V). ***Allowable Subject Matter***

Claims 55-59, 61-66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Sp/July 20 2002.